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Association between White Matter Ischaemia and Carotid Plaque Morphology as Defined by High-resolution In Vivo MRI

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Abstract *Objectives and design:* Both carotid plaque morphology and severity of white matter ischaemia (WMI) have been shown to be independent predictors of stroke risk. This study tests the hypothesis that there is an association between carotid plaque morphology as determined by high-resolution carotid MRI and WMI.
Materials and methods: Forty patients (80 arteries) with at least 40% stenosis on screening Doppler ultrasound were recruited and underwent high-resolution axial carotid MRI at 1.5 T. In a blinded manner, plaque characteristics such as lipid core, fibrous cap, intraplaque haemorrhage, lumen area, plaque area, and American Heart Association (AHA) classification were qualitatively and quantitatively evaluated. The severity of WMI was independently quantified using a modified Scheltens score based on standard brain Fluid-Attenuated Inversion Recovery. Linear mixed effect models were used to test if carotid plaque characteristics could independently predict severity of WMI.
Results: Hypertension ($p = 0.005$) and previous a history of transient ischaemic attack or stroke ($p = 0.038$) were found to be significant predictors of severity of WMI. After accounting for confounding variables, no significant association was found between the modified Scheltens score and lipid core size ($p = 0.122$), fibrous cap status ($p = 0.991$), intraplaque haemorrhage ($p = 0.708$), plaque area (0.835), lumen area (0.371) or an AHA Type VI complex plaque ($p = 0.195$).
Conclusions: Carotid plaque morphology as defined by MRI does not independently predict severity of WMI.
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Introduction

In patients with carotid atherosclerotic disease, there is growing evidence to suggest that specific plaque characteristics such as thin or ruptured fibrous caps, large necrotic lipid core or intraplaque haemorrhage may be associated with an increased risk of thrombo-embolic complications.[1,2] Such vulnerable features can be detected in vivo using high-resolution axial MRI of the carotid bifurcation and have been associated with an increased risk of subsequent neurological complications.[3–6] The validation, inter-observer variability and reproducibility of this imaging technology have been widely published.[7–9] White matter ischaemia (WMI) is commonly seen on cranial imaging in elderly individuals and its severity has been shown to be an independent risk factor for stroke risk.[10,11] An association between unstable carotid plaques based on histological analysis of excised carotid endarterectomy specimens and WMI has been previously reported suggesting that thrombo-embolic activity may partly contribute to the development of WMI.[12] The main aim of this study was therefore to explore any potential association between carotid plaque characteristics as defined by high-resolution in vivo MRI and severity of WMI.

Materials and Methods

Patients

We prospectively recruited 40 patients (4 women, median age 73.5, inter-quartile range 66–77) with at least 40% carotid stenosis as identified by Doppler ultrasound (DUS). 21 patients were symptomatic, having suffered at least 1 episode of transient ischaemic attack (TIA) or stroke in the past 6 months. The remaining clinically asymptomatic patients had been referred on the basis of either incidental carotid bruits or carotid stenosis detected on screening DUS in the course of other investigations. Other demographics were as follows: hypertension (87.5%), diabetes (12.5%), positive smoking history (70%) and atrial fibrillation (7.5%). The study was approved by the Local Ethics Committee and all patients gave informed written consent.

Imaging protocol

All patients underwent MRI on a 1.5 T whole body clinical machine (CV/I, GE Medical Systems, Milwaukee, WI). Carotid MRI was performed using a custom-designed four-channel phased array surface coil (Flick Engineering Solutions BV, Winterswijk, The Netherlands) wrapped around the neck. Our standardised protocol has been previously described in detail[4,6,13] but in brief, consisted of 2-D ECG-gated blood-suppressed fast spin echo pulse sequences with the following weightings: (a) intermediate T2W (repetition time/echo time: 2 × RR/46 ms) with fat saturation (b) T2W (repetition time/echo time: 2 × RR/100 ms) with fat saturation, (c) T1W (repetition time/echo time: 1 × RR/7.8 ms) with fat saturation and (d) Short Tau Inversion Recovery (STIR) (repetition time/echo time/inversion time: 2 × RR/46/150 ms). The field of view was 10 × 10 cm and matrix size 256 × 256 with an in-plane spatial resolution of 0.39 × 0.39 mm.

Brain imaging consisted of routine standard Fluid-Attenuated Inversion Recovery (FLAIR) and diffusion-weighted MR sequences.

Image analysis

High-resolution carotid MRI

All images were reviewed on a standard workstation by two experienced readers in consensus, in a randomized order and blinded to clinical details/brain MRI findings. Both qualitative and quantitative evaluation was made using custom image analysis software (CMRtools, Imperial College, UK). Full methodology of the image analysis protocol has been previously described[4,6,13] but in brief, for each artery, analysis was performed at the site of maximal stenosis. All MR sequences were reviewed for subjective characterisation. The state of the fibrous cap was subjectively characterised as thick, thin but intact or ruptured. Fibrous cap rupture was deemed present if there was a clear defect, discontinuity or ulceration within the fibrous cap, with or without associated thrombus or haemorrhage. The presence or absence of intraplaque haemorrhage or thrombus and lipid core was noted.

Moreover, each MRI section was classified according to the modified American Heart Association criteria: Type I/II (near-normal wall thickness, no calcification), Type III (diffuse intimal thickening or small eccentric plaque with no calcification), Type IV/V (plaque with a lipid or necrotic core surrounded by fibrous tissue with possible calcification), Type VI (complex plaque with possible surface defect, haemorrhage or thrombus), Type VII (calcified plaque) and Type VIII (fibrotic plaque without lipid core and possible small calcifications).[14]

For quantitative evaluation, a number of parameters were measured including lumen area, external vessel wall area, lipid core area; all measurements were made using the STIR sequence as previous work had shown that it was the best sequence to distinguish between the fibrous cap and lipid core components.[4,6,13] External vessel wall area was defined as the total area enclosed by the external adventitial wall. Plaque area was calculated by subtracting lumen area from the external vessel wall area. Area stenosis was calculated as the percentage of the external vessel wall area occupied by plaque area. Lipid cores occupying more than 25% of the plaque area were defined as large lipid cores.

White matter ischaemia

The severity of WMI was evaluated using a modified Scheltens score on FLAIR imaging by a third independent and blinded experienced reader. The method, as described by Scheltens et al., was modified to exclude the posterior cerebral artery territory.[15] Thus, each cerebral hemisphere was rated on a total scale of 0–54 (peri-ventricular hyperintensities: 0–6, white matter lesions: 0–24 and basal ganglia lesions 0–24). In addition to WMI, the presence of cortical and lacunar infarcts was also noted, based on the FLAIR and diffusion-weighted MRI.

Statistical analysis

We first tested for univariate associations between the modified Scheltens score and independent risk factors

Table 1 Observed associations between the modified Scheltens score and individual independent risk factors (*Pearson's correlation, †Student's *T*-test).

	Modified Scheltens score			
	Pearson's correlation (*r*)	Mean difference	95% CI	*P*-value
Age	0.211	n/a	−0.009, 0.411	0.061*
Sex	n/a	1.7	−2.7, 5.9	0.421†
Body mass index	−0.047	n/a	−0.272, 0.184	0.693*
Hypertension	n/a	5.7	4.2, 7.3	<0.001†
Diabetes	n/a	3.2	0.4, 6.0	0.002†
Smoker or previous smoker	n/a	0.6	−2.0, 3.2	0.696†
Previous TIA/stroke	n/a	4.3	1.5, 6.9	0.004†

such as age, sex, body mass index, hypertension, diabetes, smoking history and either having a previous TIA or stroke. Any risk factor with a *p*-value of <0.10 was incorporated into a linear mixed effects (LME) regression model.[16] To account for associations between two carotid arteries from the same patient, as they clearly share identical genetic and environmental vascular risk factors, our LME analysis models the patient as a random effect and thereby imposes a correlation structure on the two measurements (both left and right side) taken from the same patient. This model iteratively tested for associations between a total of 10 carotid plaque characteristics, including: haemorrhage, fibrous cap, percentage stenosis and lipid core. Each plaque characteristic was added using forward stepwise regression; after each iteration the residuals were plotted to inspect the validity of the results. A log transformation was used to make the Scheltens score meet the normality assumption. For the LME analysis a significance level of 5% was defined as statistically significant. The final LME forward regression step only incorporated the remaining risk factors with a significance of $p < 0.10$. The analysis was performed using the statistical programming language R version 2.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) using the linear and nonlinear mixed effects package (version 3.1-88).

Results

80 carotid arteries and modified Scheltens score for the 80 corresponding cerebral hemispheres were included for analysis. The distribution of arteries in terms of percentage area stenosis was as follows: 0—29% (11/80), 30—49% (9/80), 50—69% (23/80) and 70—99% (37/80). 21 carotid arteries were clinically symptomatic and a further 11 arteries had one or more silent lacunar or cortical infarcts detected on MRI in the vascular territory of interest. The remaining 48 arteries were thus defined as truly asymptomatic. The median Scheltens score was 8 (inter-quartile range 6—11).

Results of the initial univariate analysis are shown in Table 1. Age, hypertension, diabetes and a history of previous TIA or stroke were found to be statistically significant and thus incorporated into the multivariate model. The results from each forward stepwise regression within the multivariate model are shown in Table 2. We found no statistically significant association between any qualitative or quantitative carotid plaque parameter with the severity of WMI as measured by the modified Scheltens score, the final forward regression step confirmed hypertension ($p = 0.005$) and either a previous TIA or stroke ($p = 0.038$) to be statistically significant associations with WMI severity. The relationship between the

Table 2 LME regression probability values for carotid plaques morphology metrics as a predictor of white matter ischaemia (defined and graded by the modified Scheltens score). The model accounts for known covariates: age, hypertension, diabetes, or a previous history of either a stroke/transient ischaemic attack.

	Scheltens score	Additional predictors of Scheltens score			
		Age	Hyper-tension	Diabetes	Stroke/TIA
Lipid core (mm^2)	0.122	0.501	0.022	0.246	0.039
Lipid core (%)	0.101	0.457	0.020	0.261	0.047
Large lipid core (>25%)	0.297	0.486	0.019	0.252	0.040
Haemorrhage	0.708	0.595	0.019	0.200	0.050
Fibrous cap appearance	0.991	0.583	0.020	0.243	0.049
Plaque area (mm^2)	0.835	0.572	0.019	0.184	0.043
Lumen area (mm^2)	0.371	0.578	0.019	0.203	0.047
Stenosis (%)	0.251	0.585	0.019	0.205	0.043
AHA Type IV/V	0.195	0.540	0.022	0.170	0.052
AHA Type VI	0.537	0.585	0.017	0.210	0.039

modified Scheltens score and the main plaque characteristics is shown in Fig. 1 and include percentage lipid core (1a), haemorrhage (1b), fibrous cap status (1c), and the modified AHA score (1d). These figures are in keeping with the studies findings illustrating the lack of association between plaque components and WMI in our study.

Discussion

WMI is frequently seen in older people and is generally thought to reflect a process of ischaemic demyelination, predominantly related to small vessel disease.[17] WMI is not only associated with arterial hypertension, diabetes, previous strokes and other vascular risk factors but has also been shown to be an independent predictor of subsequent strokes.[18] In patients with internal carotid stenosis enrolled in the North American Symptomatic Carotid Endarterectomy Trial, the presence of WMI was associated with an increased risk of any stroke and of a disabling or fatal stroke and a worse prognosis.[19] WMI is clearly bilateral, yet it does not appear to be completely symmetrical and hence it seems of interest to explore its relationship with carotid morphology.

Variable degrees of associations between WMI severity and carotid atherosclerosis, as determined by ultrasound, have been reported. In a population-based study, De Leeuw et al. reported on an increase in the severity of periventricular but not of sub-cortical white matter lesions with an increasing number of carotid plaques.[20] Pico et al. showed that after adjusting for age, gender, and hypertension, the presence of carotid plaques at baseline, as determined by ultrasound, was significantly associated with the presence of severe WMI four years later.[21]

Few studies have, however, examined the association between WMI and carotid plaque characteristics, which are increasingly thought to be better predictors of stroke risk than luminal stenosis per se. In the Cardiovascular Health Study, WMI was strongly associated with carotid-intimal media thickness but not with carotid plaque characteristics as detected by ultrasound, after adjustments for confounding variables.[22] However, in contrast to the above study, Altaf et al. found a significant association between the morphology of carotid plaque specimens, as determined by histological analysis of excised carotid specimens and the severity of WMI.[12] Unstable carotid plaques, as defined by AHA classification, were associated with an increased number but not volume of white matter lesions. The authors concluded that thrombo-embolic plaque

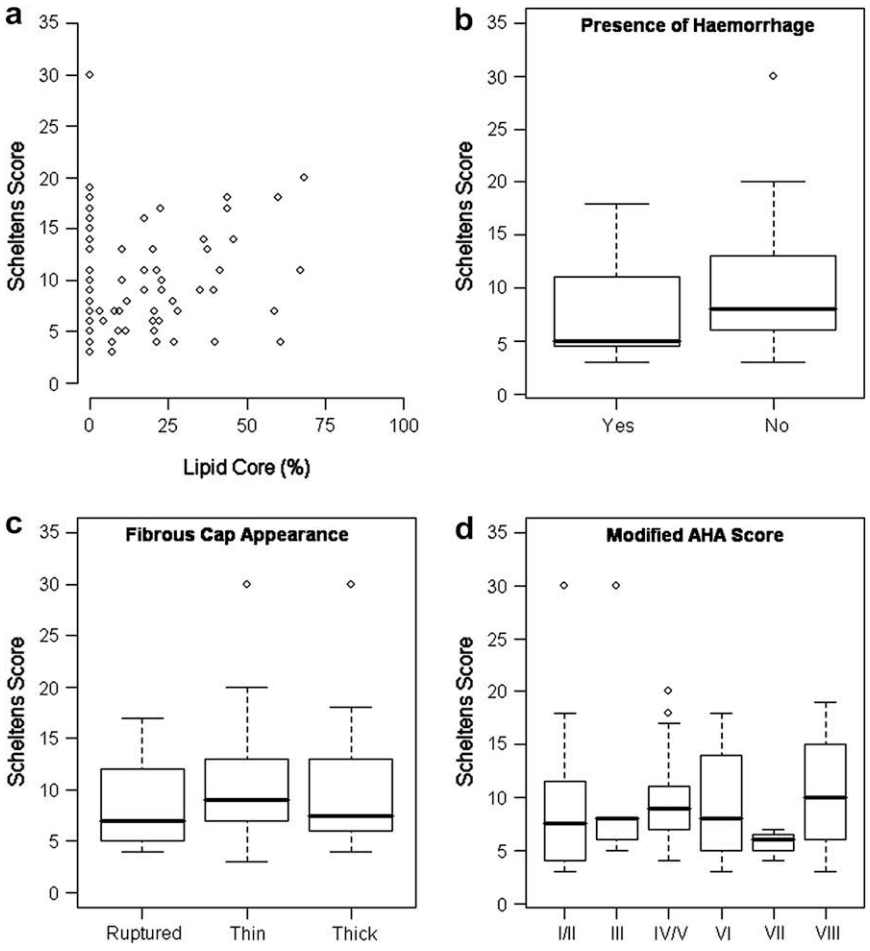

Figure 1 Relationships between white matter ischaemia as quantified by the modified Scheltens score and carotid plaque characteristics.

activity from the carotid bifurcation may contribute to the development of WMI. Recently, the advent of high-resolution MRI has allowed the robust morphological characterisation of carotid plaques in vivo. Using a limited MRI protocol, Ouhlous et al. found that the presence of lipid cores on carotid MRI correlated with the presence of infarcts on cranial MRI but not with the severity of WMI.[23] Our findings confirm and add to those of Ouhlous et al.; no significant association between any of the additional carotid vulnerable plaque characteristics and severity of WMI was detected. A possible explanation for the discrepancy between our results and those of Altaf et al. is that they used only the symptomatic diseased vessel of interest and the corresponding cerebral hemisphere in their analysis and ignored the contralateral cerebral hemisphere.[12] It is difficult to reconcile this approach with the bilateral and symmetrical nature of WMI. In our opinion, it is difficult to explain why contralateral cerebral hemispheres distal to near-normal or mildly diseased carotid arteries would have WMI, similar in extent to more severely diseased carotid arteries, if there was a direct causal thrombo-embolic association between carotid atheroma and WMI.

This study did not report a control group as it seemed unintuitive to impose an arbitrary cut-off to the plaque characterisation. The study does however include a mix of both symptomatic ($n = 21$) and asymptomatic ($n = 19$) subjects. The univariate analysis finds that a history of previous TIA or stroke was significantly associated with the WMI score ($p = 0.004$, mean difference 4.3, 95% confidence interval 1.5—6.9).

A linear mixed effects model was applied in the multivariate statistical analysis to account for the correlation structure between WMI scores from both hemispheres and the left and right carotids. Statistical inference was then computed after accounting for this correlation, thus accounting for the dependence of the multiple measurements from the same patient.

A potential limitation of our study is that we were unable to examine the relationship of plaque calcification with WMI due to the limitations of MRI to detect calcification. However, a study by Fanning et al. found no association between plaque calcification on CT and severity of WMI.[24]

This study does find associations between WMI and traditional cardiovascular risk factors which concurs with the previously reported findings. No association was however observed between the AHA-graded complex plaques and WMI scores as previously demonstrated by Altaf et al.[12] This discrepancy could be due to a Type II error i.e. a failure to detect an association when in fact an association exists. However, this study also goes beyond the findings published by Altaf and found that none of the additional plaque characteristics measured using MRI were associated with WMI. Altaf's study cohort was composed of patients with high degrees of carotid stenosis and the plaque classification was graded based on histological examination. Therefore the study was limited by ethical considerations as surgical intervention was only performed on patients with advanced disease. The study finding reported here suggests that the findings from Altaf et al. cannot be extended to reflect the general population. However, it will ultimately require further follow-up studies to establish this.

Conclusions

Carotid plaque composition, as defined by MRI, does not independently predict the severity of WMI.

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Competing Interests

Andrew J. Patterson: n/a
Jean Marie Gillard: n/a
Tjun Y. Tang: n/a
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